What to do with the patient with a positive HCV antibody test

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A test to measure hepatitis C antibody has recently been developed. The development of the antibody test was closely followed by the publication of two trials which demonstrated the efficacy of interferon alfa in the treatment of transfusion-associated hepatitis C. The author discusses management of the patient with a positive hepatitis C virus (HCV) antibody test, including an approach to sorting out those patients who have false positive tests, information about modes of transmission for those patients who are asymptomatic carriers, and guidelines to determine which patients may be candidates for interferon therapy.

Physicians will begin to hear from more and more patients who have been found to have antibody to hepatitis C virus. These individuals understandably will be concerned about the implications of their positive test. It is the obligation of their personal physicians to address that concern, decide whether further investigation is necessary and plan an evaluation when it is appropriate. It is the purpose of this article to make this task easier.

There are two test kits used by the main laboratories in Hawaii to determine the presence of HCV antibody. They are made by different manufacturers. The Ortho Diagnostic Systems (ELISA) assay is used by the Blood Bank of Hawaii; the Abbott Labs (EIA) assay is used by Diagnostic Laboratory Services (DLS); and by SmithKline Beecham (Accupath) Labs.

Although the mechanics of how the tests are performed are different, both kits are based on work done at Chiron Corporation laboratories. In 1989 researchers there reported the isolation of non-A non-B (NANB) hepatitis viral RNA, made cloned DNA, produced polypeptide that coded by this DNA and identified antibody against this polypetide in patients with NANB hepatitis[1,2]. The commercially available test kits use an enzyme-linked immunoassay technique to identify circulating antibody to this HCV specific polypeptide.

There are several important facts to be realized about the anti-HCV test:

1) Antibody to HCV develops in approximately 50% of patients with acute hepatitis C and most lose the antibody after the acute illness resolves. In contrast, patients with chronic hepatitis C have persistent antibody. Thus, the presence of antibody to HCV does not generally represent immunity, but more often suggests chronic infection[3,4,5].

2) There is a significant false positive rate. As many as 30 to 60% of positive ELISA tests found among blood donors in Hawaii are thought to be false positives[6]. Furthermore, patients with autoimmune hepatitis and paraproteinemias are said to have a high frequency of false positive tests[7,8,9].

3) There is a significant false negative rate. Approximately 20% of all cases of post-transfusional hepatitis will have a negative test for HCV antibody. Part of this 20% is accounted for by another hepatitis virus (neither A, B, nor C), but it is clear that the HCV antibody test may fail to identify patients who unequivocally have hepatitis C. There are at least two reasons this occurs. Some patients may take up to one year, or fail altogether, to develop HCV antibody despite having epidemiologic evidence of having post-transfusional hepatitis C. Alternatively, the available commercial assays may be insufficiently sensitive to identify individuals with low titers of antibody[4,10].

The problem of false positive ELISA tests has lead to the development of other techniques to identify and confirm anti-HCV positive patients. The best studied of these is the recombinant immunoblot assay (RIBA) which has not yet been approved for clinical use by the FDA. Reports suggest that patients who are ELISA and RIBA positive are more likely to have HCV hepatitis than patients who are positive for the ELISA assay only[11,12].

However, it is important to realize that both false positives and false negatives may occur despite the results of the ELISA and RIBA assays. The Blood Bank of Hawaii automatically sends all ELISA positive specimens to a reference lab for RIBA testing. DLS found that specimens strongly positive on the initial EIA assay, in their patient population, nearly always had positive supplemental tests and, therefore, it sends only specimens which are weakly positive on EIA for additional testing. SmithKline Beecham does not do supplementary testing for specimens found positive on the initial EIA assay.

So what are we to do with the patient who is found to be HCV positive?

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The first step is to do a careful history and physical examination in looking for risk factors for HCV and signs and symptoms of chronic liver disease. A history of prior blood product transfusion, i.v. drug use, multiple sexual partners or sexual contact with a person with hepatitis, membership in a household where another individual has hepatitis, as well as employment as a health-care worker, have all been suggested as risk factors for HCV.

The second step is to determine the serum ALT. If there are no apparent risk factors for hepatitis C; if the ALT is normal and if RIBA testing was negative, the most likely explanation is that the HCV antibody test was a false positive. However, because hepatitis C is typically associated with irregular elevations of transaminases, and since liver disease has been observed to occur in patients with transiently normal ALTs; one should repeat the ALT every 3 months (Esteban-Mur JI, Second International Symposium on HCV, Los Angeles, November 1990). If the ALT is persistently normal for a year, no further follow-up is needed.

In the same case (anti-HCV positive, normal ALT), if the RIBA test was positive, the patient may have recovered from hepatitis C but unlike most patients, has persistent antibody. Alternatively, the patient may be an asymptomatic carrier. The appropriate response is to monitor the ALT periodically to be sure that it is persistently normal.

One should also advise that the patient may be an infectious carrier in order to educate him or her about presumed modes of transmission. We know that parenteral transmission is the most frequent, but other modes of transmission must exist, as at least 40% of patients do not have a recognized risk factor for hepatitis C[13].

The role of sexual transmission is unclear. The homosexual population does not appear to be at increased risk for HCV hepatitis and spouses of patients with hepatitis C do not have a higher than expected rate of antibodies to HCV[14,15]. On the other hand, there is a report that more patients with NANB hepatitis have a history of multiple sexual partners or sexual contact with someone with a history of hepatitis than does a control population[16]. Thus it is prudent to advise patients to use safer sexual practices until further information is available.

Maternal-neonatal transmission has been reported to occur 50% of the time but does not result in chronic hepatitis in the infant[17], as reported by Roggendorf at the Second International Symposium on HCV.

When the patient is anti-HCV positive and has an abnormal ALT, other causes of liver disease must be sought because of the chance of a false-positive antibody test. Diseases that should be considered include hepatitis B, hemochromatosis, Wilson's disease, alpha 1 antitrypsin deficiency, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, drug hepatotoxicity, fatty liver, alcohol-induced liver disease, thyroid disease, syphilis and infiltrating processes. Appropriate serologic tests and an imaging study such as ultrasound or CT-scan should be considered. The patient should have ALTs rechecked every 2 months. If the ALT returns to normal and stays normal over the course of a year, the patient may have recovered from hepatitis C, or may have become a chronic asymptomatic carrier. These patients need

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to receive the information about disease transmission as described above and should have a repeat ALT every 6 to 12 months.

What then about the patient who is HCV positive and has a persistently or intermittently abnormal ALT over a period greater than 6 months? If a thorough evaluation has ruled out other causes of liver disease, and the patient has a positive RIBA test, it may be assumed that the patient has chronic hepatitis C. The question then becomes what if anything should be done about it? To answer this, one must first understand the natural history of untreated chronic hepatitis C and what potential treatment there is to offer.

We know that at least 20% of patients with chronic hepatitis C will eventually develop cirrhosis[13]. Furthermore, there is increasing evidence that chronic hepatitis C is associated with the development of hepatoma[18,19]. Treatment that eliminates the carrier state is the ultimate goal and would theoretically prevent the development of cirrhosis and hepatocellular carcinoma. Until recently, there was no test for the presence of viral RNA (although PCR technology has made this now possible on a research basis). Investigators therefore have relied on a normal ALT and improvement in hepatic histology as markers of successful treatment.

Studies on treatment with acyclovir and steroids in patients with chronic NANB hepatitis have found that neither drug is effective[20,21]. On the other hand, 2 randomized controlled trials have recently shown that interferon is effective in controlling disease activity in a significant number of patients with chronic hepatitis C[22,23]. These trials used interferon at doses of 1, 2, and 3-million units given 3 times weekly for 24 weeks. The response rates (normalization of serum ALT) were 28%, 48%, and 46% respectively with a 10% placebo response.

Improvement in liver histology was also seen. Unfortunately, only 20 to 50% of those whose ALT values become normal, maintained those values over the 6 to 12 month follow-up after treatment ended. Side effects were common and included flu-like symptoms, diarrhea, mild alopecia and occasional thrombocytopenia; but dose reduction or withdrawal from the study was rarely required. Future trials will focus on finding the ideal dose and duration of treatment to improve response rates and remission maintenance.

The patient with chronic hepatitis C should, therefore, be advised not only how to prevent further transmission of the disease but also of the option of treatment with interferon. Some clinicians would argue that the long-term effects of treatment with interferon for this disease are not well enough known to be recommended for anyone (Koretz RL, comment in *Hepatology* 1990; 12:613-615). However, the FDA has recently approved interferon for use in hepatitis C. Given the significant incidence of an adverse outcome in untreated disease, many patients will wish to consider this potentially beneficial treatment for themselves.

Which patient with hepatitis C is a candidate for treatment with interferon? Treatment criteria at a minimum should include: A pretreatment liver biopsy that shows chronic persistent or chronic active hepatitis and/or cirrhosis; at least 6 months of documented elevation of ALT greater than 1.5X normal; careful exclusion of other causes of liver disease; no history of CNS trauma, depression or other major medical illness; a normal creatinine; age greater than 18 and not pregnant; HIV and HBsAg negative, WBC >3,000, platelet count >70,000, stable liver disease (ie, no evidence of ascites, encephalopathy or variceal bleeding, bilirubin <2.0, prothrombin time <3 seconds greater than control); normal TSH and T4, and HCV antibody-positive confirmed by RIBA.

Should a decision to treat be made, the Davis and Di Bisceglie trials suggest that 3-million units of interferon be administered subcutaneously 3 times a week as the appropriate treatment regimen.

However, the optimal dosage of interferon has yet to be defined. No one knows yet how the drug will work in Hawaii's ethnically diverse population, and there are no data on what to do for those who fail to respond initially or who relapse on termination of therapy. Furthermore, the drug carries with it potential toxicity, and much remains to be learned about the natural history of treated and untreated disease.

We believe, therefore, that physicians who plan to use interferon on patients should follow specific treatment guidelines, enroll patients in controlled trials when such trials are available, and that data on patients should be collected and recorded in order to help answer the many questions about hepatitis C and its treatment.

The Liver Research Group of Hawaii was created to answer this need (see the appendix below).

APPENDIX

In the fall of 1990, a group of physicians interested in the treatment of patients with liver disease came together and, with assistance from the Cedars-Sinai Medical Center in Los Angeles and the Cancer Research Center of Hawaii, formed the Liver Research Group. It is the intent of this group to make the latest treatments for chronic liver disease available to patients in Hawaii. The Liver Research Group encourages physicians who take care of these patients to contact its office at the Cancer Research Center (548-8545) for further information about enrolling patients in clinical trials or obtaining specific guidelines for the use of recently approved treatments such as interferon in chronic hepatitis C.

The 1990s have seen an explosion of knowledge about Hepatitis C. We now have potentially an exciting treatment for this previously untreatable condition. We in Hawaii are in a position to add to this fund of knowledge as well as offer our patients state-of-the-art care. However, we must recognize our responsibility to "first do no harm", treat according to the best scientific principles, and where knowledge is deficient, to collect data so we can care for future patients more effectively.

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For readers interested in further information, the charter of the Hawaii Liver Research Group follows:

Chronic Liver Disease Research Group

The Chronic Liver Disease Research Group will be established to foster the study of treatment and prevention of chronic liver disease and its consequences. Of particular interest to the group are treatments which interrupt the progression of chronic viral hepatitis to cirrhosis and hepatocellular carcinoma. The group will also help advise those individuals involved in the care of patients who are candidates for liver transplantation.

Background:

The initial funding for the research group has been made possible by a donation from the Cedars-Sinai Medical Center. This funding includes money for salary and overhead for a nurse study coordinator. The nurse coordinator will be based at the Cancer Research Center in Honolulu, Hawaii.

The need for such a research group is clear. 1) Hawaii's unique ethnic diversity, relative geographic isolation and high carrier rate for hepatitis B, make it an ideal place to study the effects of potential treatment and natural history of chronic liver disease. 2) Several potential treatments for liver disease for which we have had nothing to offer before, are now in the process of development. These treatments are promising enough that they should be made available at the earliest possible time to patients in Hawaii. However, these treatments should be conducted in the setting of clinical trials until enough data has been generated to standardize their use. 3) No center is now performing liver transplantation in Hawaii. There is a need for a central repository of information about Mainland transplant centers. There is also a need to have personnel familiar with the pre-transplant screening process and mechanics of referral for liver transplantation. This would allow for the best use of the health care facilities in Hawaii before referral to Mainland centers for transplantation.

Structure

A nurse coordinator will be hired. This individual will be responsible for maintaining records of ongoing research protocols. The nurse coordinator will remain in contact with the originating investigator. By going to physician offices, helping to draw blood if necessary and gathering data from the individual physicians, the N-C will facilitate the broader availability of treatment protocols while making it possible to study treatment strategies in a useful and meaningful way. The N-C will make sure that the protocols are being followed correctly and will send data to the original investigator. The N-C will be responsible for making the availability of research protocols widely known to physicians in the community. The N-C will help in processing protocols through any appropriate institutional review board.

The activities of the nurse will be supervised by the chairman of the Chronic Liver Disease Research Group. This chairman will be appointed by committee. The committee will be composed of interested individuals representing a broad spectrum of physicians involved in the treatment of patients with chronic liver disease. In addition to electing a chairman, the committee will encourage investigators to submit research protocols for approval. Approved protocols will be eligible for assistance from the N-C. The committee will approve protocols on the basis of the following priorities:

1) Scientific merit.

2) The applicability of the research to patients in Hawaii.

3) The uniqueness of the research proposal.

4) The potential benefit of the treatment. As an example: a proposal for a promising treatment in a condition for which there is now no effective treatment would receive a priority rating.

5) The proposal must have received approval from an institutional review board most appropriate to the individual(s) originating the proposal.

A reassessment of ongoing protocols at 6 months will be undertaken by the committee to ensure that the original approval is still appropriate.

Final comments

The funding for this organization has come from the Cedars-Sinai Medical Center. Academic support and a number of research protocols will also be provided by Cedars-Sinai Medical Center. However, the committee will consider proposals from other investigators in Hawaii and from other institutions based on the elements described above. Should patients involved in treatment protocols require liver transplantation, the personal physician will retain the right to refer the patient for whatever treatment and to whatever institution the physician feels is in the best interest of the patient.

The funding is for one year. At the end of that time the relationship with Cedars-Sinai Medical Center and the performance of the liver research group will be reevaluated. It is hoped that this relationship will have been a productive one and that the funding and academic support will be continued. It is also hoped that other sources of funding may also be found which would allow for a greater scope of activity, and the creation of a permanent entity, The Liver Research Center.

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